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The World Reference Center for Arboviruses and Retroviruses received viruses from the United States and foreign countries for characterization and identification. New viruses, or viruses causing diseases not previously recognized included a subtype of Cache Valley virus from a febrile military recruit, LaCrosse virus from encephalitic dogs, Kagoshima and Cache Valley viruses associated with fetal abnormalities of livestock, and new phleboviruses from tropical America and West Africa. Genetically engineered flavivirus trpE proteins reacted specifically by ELISA. The cell lysate antigen technique for ELISA was adapted to a large number of arboviruses. ELISA was also developed for rapid testing of 17D yellow fever vaccinees. Limited primer extension sequencing of dengue and Japanese encephalitis viruses showed that their genotypes were geographically focal. The method was used to demonstrate the origin of an introduced dengue virus. Retrovirus isolation capability was developed and a novel enveloped agent from tissues of Kaposi sarcoma patients was studied serologically. Reference reagents were distributed to scientists in over 20 countries.

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ABSTRACT

The World Reference Center for Arboviruses and Retroviruses received viruses from the United States and foreign countries for characterization and identification. New viruses, or viruses causing diseases not previously recognized included a subtype of Cache Valley virus from a febrile military recruit, LaCrosse virus from encephalitic dogs, Kagoshima and Cache Valley viruses associated with fetal abnormalities of livestock, and new phleboviruses from tropical America and West Africa. Genetically engineered flavivirus trpE proteins reacted specifically by ELISA. The cell lysate antigen technique for ELISA was adapted to a large number of arboviruses. ELISA was also developed for rapid testing of 17D yellow fever vaccinees. Limited primer extension sequencing of dengue and Japanese encephalitis viruses showed that their genotypes were geographically focal. The method was used to demonstrate the origin of an introduced dengue virus. Retrovirus isolation capability was developed and a novel enveloped agent from tissues of Kaposi sarcoma patients was studied serologically. Reference reagents were distributed to scientists in over 20 countries.

FOREWORD

In conducting the research described in this report, the investigators adhered to the "Guide for the Care and Use of Laboratory Animals," prepared by tthe Committee on Care and Use of Laboratory Animals of the Institue of Laboratory Animal Resources, National Research Council (DHEW Publication No. (NIH) 86-23, Revised 1985).

For the protection of human subjects the investigators have adhered to policies of applicable Federal Law 45CFR46.

BODY OF REPORT:

Introduction. The World Reference Center for Arboviruses was established at the Yale Arbovirus Research Unit in 1965 as an outgrowth of The Rockefeller Foundation program on arboviruses which was moved in 1965 to Yale University from New York City. The U.S. Army has supported this program since 1972, initially through joint Navy-Army funding, then through separate contracts and grants, and during the past three years by this grant. The progress of the past three years is included in this report; it covers the work for the entire project which received support from WHO and NIH in addition to that of this grant.

Virus identification. Viruses were identified from the United States and from Panama, Angola, Czechoslovakia, Indonesia, Ivory Coast, Viet Nam, Thailand, Taiwan, Japan, and Brazil. Among these were:

BUNYAVIRUSES. A virus isolated from blood of a febrile U.S. Army recruit on jungle training in Panama was identified as a subtype of Cache Valley virus.

PHLEBOVIRUSES. Eight new phleboviruses were characterized serologically. Odenisrou, a new phlebovirus from the Ivory Coast, was also characterized serologically.

ORBIVIRUSES. A Palyam group virus, Kagoshima, was identified from Culicoides midges from Japan for the first time. This virus was associated with congenital abnormalities in livestock. The virus was shown to be the same as Kasba virus from India.

POXVIRUSES. Ectromelia virus was found in viruses from Czechoslovakia submitted for identification.

Classification of arboviruses. Studies of two serogroups in the genus Orbivirus led to a proposal for defining species. The correlation between the degree of RNA-RNA hybridization and genetic reassortment of these double stranded RNA viruses was excellent.

Diagnosis of disease. Cache Valley virus was associated with an epizootic in sheep of arthrogryposis and hydranencephaly affecting nearly 20% of offspring in Texas and Nebraska. This is the first time a bunyavirus has been implicated in this disease in the Americas.

A virus was isolated by scientists of the University of Georgia from two puppies in rural Georgia. The puppies died of encephalitis. Neutralization tests confirmed the identity of the virus as LaCrosse virus, a cause of human encephalitis. This is the first time this virus has been isolated in nature from encephalitic dogs.

An outbreak of hemorrhagic fever in Pakistan was studied. Although seroreactivity in one patient to Crimean-Congo hemorrhagic fever virus was detected, this virus was apparently not the only cause of the illness.

Characterization of monoclonal antibodies. Monclonal antibodies were developed and characterized for vesicular stomatitis (VSV), Indiana, Cocal, and Alagoas viruses. These were field tested for their diagnostic specificity at the Foot and Mouth Disease Laboratory in Rio de Janeiro.

Semliki Forest virus monoclonal antibodies were used to find a conserved epitopic region on the alphavirus nucleocapsid protein. A mixture of monoclonal antibodies to Semliki Forest virus was blended to develop a sensitive antigen capture ELISA for alphaviruses.

Development of new techniques. Flavivirus trpE fusion proteins were used as highly specific diagnostic reagents in ELISA. A region of the flavivirus RNA, coding for an antigenic domain that is relatively serotype specific, was located between amino acids 300 and 400 of the E protein. Fusion proteins corresponding to this region were produced for Japanese encephalitis and dengue-1 using previously cloned cDNA. Analagous protein for dengue-2 virus was made using the polymerase chain reaction technology and primers derived from published sequences. The fusion proteins were coated directly on the solid phase for use as ELISA antigens. These proteins were not very immunogenic to mice, but were useful in distinguishing among flaviviruses using antibodies raised in mice.

The yellow fever ELISA was adapted to test 17D vaccinees who were immunological virgins for flaviviruses. The ELISA was as sensitive as the plaque reduction neutralization test (PRNT). ELISA showed seroconversion earlier than PRNT in many cases.

Human-pathogenic arboviruses were adapted to a rabbit kidney continuous cell line that used medium containing rabbit sera, in order to develop a system of immunizing rabbits free of heterologous species reactivity. The immune rabbit sera were used in ELISA as coating antibody to capture antigen.

A rapid method of raising murine antibodies utilized intrasplenic inoculation of mice. Antibody was detected by ELISA as early as 3 days post inoculation, and consistently by the fifth day post inoculation.

The utility of the cell lysate method of producing antigens was confirmed. This technique was originated at USAMRIID. Comparison of results of Rift Valley fever cell lysate antigen with conventional mouse liver antigen in tests of human sera from Ethiopia showed a high degree of correlation.

Molecular epidemiology. Limited primer extension sequencing of dengue-1, dengue-2, and Japanese encephalitis viruses has shown geographic clustering of each of these flaviviruses. Forty-six isolates of Japanese encephalitis virus from various sources and localities in Asia were examined for genetic diversity. The isolates segregated into three geographic patterns. One pattern encompassed southern Thailand, Malaysia, and Indonesia and correlated with the zone that has endemic transmission without major Japanese encephalitis epidemics. It is now possible to trace the origin of new cases and of outbreaks of diseases caused by the three viruses.

A strain of dengue-1 isolated from the blood of a patient in Angola was genotyped by this technique and found presumptively to be of Caribbean, not African, in origin.

Collection of low passage arbovirus strains. A large collection of low passage arbovirus strains has been developed and maintained lyophilized. Priority was given to yellow fever, dengue, chikungunya, California encephalitis, Venezuelan encephalitis, St. Louis encephalitis, western encephalitis, eastern encephalitis, Japanese encephalitis, and other human disease arboviruses. The original (or as close to original as was available) material was passaged once in C6/36 mosquito cells or in Vero cells. The resulting stock was lyophilized in aliquots. These were stored and distributed to any and all persons requesting material for study. The collection now contains in excess of 400 strains.

Flavivirus sequence data bank. The sequences of flaviviruses are now on line in an electronic data bank and can be accessed by phone. Floppy discs containing the data were mailed to several investigators working with flaviviruses.

Studies of retroviruses. Attempts to identify by IFA a novel enveloped agent isolated from tissues of patients with Kaposi's sarcoma were negative with a large battery of arboviruses. Retrovirus (HIV) isolation capability was established using H-9 and EBV-transformed lymphocyte cell lines. Some of these lines were supplied to the Instituto Nacional de Salud in Bogota to transfer the technology.

Distribution of reagents. Reference reagents including virus stocks, antibodies, antigens, cell lines, and live insects were distributed in the United States and to scientists in more than 20 foreign nations. Data on reagents available for distribution were entered in a dBase-3+ data bank. More than 4,000 entries have been made so far.

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